SmithKline Beecham

COURIER

Our Ref: CT/P32151/EP

7 March 2000

European Patent Office
D-80298 München
GERMANY

EPO-Munich 89
08. März 2000

URGENT – For the attention of S Haertinger
Accelerated prosecution requested

Dear Sirs

European Patent Application No. 99303151.7-2117
SmithKline Beecham plc

I refer to the communication pursuant to Article 96(2) and Rule 51(2) EPC dated 7 February 2000 and have the following comments.

1. I am grateful for the Examining Division's diligence in identifying the typographical error in amended claim 3 and agree that such claim should refer to an organic acid salt of paroxetine. Enclosed in triplicate is a new page 50 reflecting this correction.

2. I am also pleased to note the acknowledgement that the current set of claims meet the requirements of unity of invention according to Art 82 EPC.

3. With regard to novelty it is submitted that claim 1 and its dependent claims 2 to 19 relate to a particular crystalline form of paroxetine methanesulfonate that has not been disclosed in D3.

   Evidence for this is provided in the attached declaration of Ian Robert Lynch who is an expert in using IR spectroscopy to identify polymorphic forms of pharmaceuticals. He is also an author of D4 referred to by the Examining Division.

   The Lynch declaration contains a table comparing the IR data quoted in D3 for paroxetine methanesulfonate with that observed for Examples 3 and 12 which are representative of all the examples of the present application. Also attached are copies of the original IR spectra obtained for Examples 3 and 12.

   The table of data (and supporting IR spectra) demonstrate that for the particular crystalline form of paroxetine methanesulfonate described in the examples of the

Corporate Intellectual Property
Two New Horizons Court, Brentford, Middlesex TW8 9EP Tel: 0181 975 2000 Fax: 0181 975 8177

present application that the same characteristic IR peaks (shown in bold) are found whether using Nujol Mull, or ATR (attenuated total reflection) or KBr discs.

Whilst D4 suggests that in the case of paroxetine hydrochloride the use of KBr discs can reduce the crystallinity of a particular polymorph, this is clearly not an issue for paroxetine methanesulfonate. Indeed substantially the same IR spectrum has been obtained by the present applicants using a variety of different techniques, indicating that the crystalline form of paroxetine methanesulfonate has not been changed by the use of KBr discs.

Therefore a comparison of the IR data obtained for the form of paroxetine methanesulfonate discovered by the present applicants with that quoted in D3 is quite legitimate and clearly demonstrates a novel crystalline form not previously described.

4. Claim 1 of the present application stipulates that the crystalline methanesulfonate has at least the following IR peaks: 1603, 1513, 1194, 1045, 946, 830, 776, 601, 554, and 539 ± 4 cm^{-1}.

   Even allowing for an error margin of ± 4 cm^{-1} (which is actually quite broad given the accuracy of modern IR spectrometers of about ± 1 cm^{-1}) only two of the above noted peaks are found in D3 (namely at 1515 and 777 cm^{-1}).

   The remaining 8 (out of 10) peaks at 1603, 1194, 1045, 946, 830, 601, 554, and 539 cm^{-1} are not found in the material described by D3 and are therefore evidently characteristic of a new crystalline form.

   The material described by D3 therefore falls outside the scope of claim 1 (it does not have 8 of the characteristic IR peaks required) and therefore can not anticipate this claim according to Art 54 EPC.

5. In view of these comments and newly submitted data it is believed that this application can now quickly proceed to grant. If, however, the Examining Division requires further clarification please contact the undersigned on +44 181 975 6347 to discuss any outstanding issues or to arrange an informal interview which may help further to expedite grant of this important application.

Yours faithfully,

Clive Thompson

Clive Thompson
Authorised Professional Representative.

Enc.

Claims

1. Paroxetine methanesulfonate in crystalline form having *inter alia* the following characteristic IR peaks: 1603, 1513, 1194, 1045, 946, 830, 776, 601, 554, and 539 ± 4 cm^{-1}.; and/or the following characteristic XRD peaks: 8.3, 10.5, 15.6, 16.3, 17.7, 18.2, 19.8, 20.4, 21.5, 22.0, 22.4, 23.8, 24.4, 25.0, 25.3, 25.8, 26.6, 30.0, 30.2, and 31.6 ±0.2 degrees 2 theta.

2. A process for the preparation of a compound as claimed in claim 1 comprising crystallizing or re-crystallizing the compound from a solution of paroxetine methanesulfonate in a solvent.

3. A process according to claim 2 in which the solution of paroxetine methanesulfonate is prepared by treating paroxetine free base or an organic acid salt thereof with methanesulfonic acid or an ammonium or amine salt thereof.

4. A process according to claims 2 or 3 in which the solvent comprises toluene, an alcohol, an ester, a ketone, a halogenated hydrocarbon, a nitrile, or an ether, optionally in admixture with water, an ether, or a lower alcohol, or mixtures thereof.

5. A process according to any one of claims 2 to 4 in which the solvent forms an azeotrope with water and prior to isolation of the product water is removed by azeotropic distillation.

6. A process according to any one of claims 2 to 5 in which the crystallisation is promoted by inclusion of an anti-solvent to the solvent, in which the anti-solvent is an ether or hexane.

7. A process according to any one of claims 2 to 6 in which the crystallisation is conducted at elevated temperature followed by controlled cooling.